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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
EWOLDT, GERALD R

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 12/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/393,652	SRIVASTAVA ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 August 2004 and 26 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 33-52, and newly added Claim 53, are being acted upon.

2. Applicant's amendment, remarks, drawings, IDS, and 1.132 declaration of Inventor Srivastava, filed 8/26/04, and drawings, filed 9/26/05, are acknowledged. In view of Applicant's amendment, the previous rejection under 35 U.S.C. 112, second paragraph, has been withdrawn. In view of Applicant's remarks, the previous rejection under 35 U.S.C. 112, first paragraph, for the introduction of new matter, has also been withdrawn.

3. The drawings filed 9/26/05 have not been found acceptable because the changes to the drawings have not been identified/indicated. Accordingly the drawings have not been entered.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 33-52, and newly added Claim 53, stand/are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method for inhibiting the rejection of BALB/CJ skin when transplanted onto a C57BL/6 mouse, said method comprising administering to a C57BL/6 mouse gp96 purified from a BALB/cJ source, said administration comprising subcutaneous injection of 100 ug 10 days prior to transplantation, repeated 3 days prior to transplantation,

does not reasonably provide enablement for:

a method for treating or preventing rejection of a grafted cell, tissue, or organ in a mammal comprising administering to a mammal a composition comprising a purified complex consisting essentially of a heat shock protein non-covalently bound to a peptide, wherein the peptide is not an alloantigen of the grafted cell, tissue, or organ.

As set forth previously, little is known regarding treating or preventing graft rejection by administering HSPs. Indeed, the Inventor himself has

repeatedly taught that in numerous contexts, both in vitro and in vivo, all heat shock proteins are immunostimulatory (see for example, U.S. Patents No. 5,985,270, 5,750,119, and 5,961,979). Accordingly, claims based on the highly unexpected assertion that HSPS are sometimes immunosuppressive when administered in vivo, require enablement commensurate with the scope of the claims.

Regarding the scope of the claims, it is noted that said claims encompass the claimed method employing all HSPs (except hsp60 and cpn10) which Applicant has repeatedly argued (and demonstrated with sequence alignments) are not related and are not interchangeable. Clearly then, given the highly unexpected nature of the instant invention, said invention cannot be considered to be enabled for any HSP not demonstrated (in the specification or art) to be immunosuppressive in the instant context (graft rejection). It is noted that the specification discloses only the use of BALB/cJ mouse and unknown rat gp96, and only in the context of transplant into a C57BL/6 mouse. The results of Experiment 2 demonstrate that rat gp96 treatment worked little (if any) better than control (no) treatment in the instant method. Accordingly, not even all gp96's (even those likely to be closely related) can be considered to be enabled. The most likely conclusion to be drawn from the limited data is that the gp96 must derive from the same genetic source as the graft.

A review of the specification discloses that the maximum disclosed dosage range is "about 5 ug to about 5000 ug" of complex (page 31). There is no disclosure in the specification of any dosage greater than "about 5000 ug" in any context. The specification also discloses that a 20-25 g mouse is administered 100-200 ug of complex; the specification also demonstrates that lesser dosages are ineffective (see Experiments 1 and 2). As a human is roughly 3000 times the size of a mouse, the appropriate dosage for a human would likely be 300,000-600,000 ug of complex - at least 60 times higher than the highest dosage disclosed by the specification. As a horse or cow is roughly 10 times the size of a human, the maximum disclosed dosage would likely fall 600 times short of what would be required to be effective in said mammals.

It is the Examiner's position then that given the broad scope of the claims and the limited working examples, the specification cannot be considered enabling for the invention as claimed.

Applicant has submitted WO 02/072133 as enablement for "HSP70 family members" in the method of the instant claims. Upon review said document cannot be considered enabling for the use of HSP70 family members in the method of the instant claims. The document discloses the use of BiP (a HSP70) only in a highly artificial arthritis model. Presumably, Applicant's argument is that artificial arthritis and graft rejection are both TH1- mediated, thus a treatment for the artificial arthritis model would be effective as a treatment for graft rejection. The document indicates that BiP has an immunosuppressive effect because it stimulates IL-10 release (page 8) which induces an anti-inflammatory shift towards TH2 (page 23). This capability of inducing IL-10 release and the subsequent shift towards TH2 is presumably how BiP might function in inhibiting graft rejection. There exists however, a significant body of work indicating that IL-10 is not necessarily immunoprotective, a shift towards TH2 is not necessarily desirable, and a HSP70 might actually be a facilitator in numerous models of TH1-mediated pathology. See for example, Pakala et al. wherein it is taught that in a disease model thought to be TH1-mediated, induction of IL-10 and a TH2 response, rather than being protective or benign, was highly pathogenic. The work calls into question the entire concept of a shift towards TH2 as a treatment of TH1 pathologies. See also McFarland, wherein as early as 1996 it was taught the "Mechanisms of autoimmunity (and presumably graft rejection) are more complicated than a simple TH1-Th2 dichotomy". The reference further teaches additional instances wherein the TH2 response worsens diseases thought to be THI mediated. As regards an HSP70 family member specifically, Mycko et al. teaches the enhancement of another TH1 mediated disease by over-expression of HSP70 and increased Class II presentation of an autoantigen. The combined references indicate that, at best, the use of a HSP70 in a

method of inhibiting a TH1-mediated response [including graft rejection] must be considered to be highly unpredictable.

In the specific context of allograft reaction, Pockley teaches that "the balance between protective and damaging effects [of HSPS] and the precise influence of these responses on graft outcome is unclear". In some instances HSPs appear to promote the development of acute and chronic graft rejection whereas in other instances heat shock proteins appear to be cytoprotective. The reference concludes that "The role of heat shock proteins in allograft immunity is unclear and more insight into the processes by which heat shock proteins encounter and are recognized by the recipient immune system after transplantation is required." Clearly then, the reference serves to define the invention of the instant claims as being unpredictable.

Applicant's arguments, filed 8/26/04, have been fully considered but they are not persuasive. Applicant cites the newly submitted 1.132 declaration of Inventor Srivastava. The declaration is considered here. Arguments not addressed in the Inventor's declaration are addressed below. The Inventor argues that gp96 has an immunosuppressive property and discloses experimental evidence in support. The Inventor argues that the data show a suppression of an anti-tumor response. An additional experiment shows CD4+-mediated suppression of diabetes in NOD mice. The Inventor concludes that "these results establish that relatively high doses of gp96 complexes have an immunosuppressive activity". The Inventor opines that graft rejection could be inhibited regardless of the species from which the gp96 is obtained and that all hsp90 family heat shock proteins can inhibit graft rejection because (in the instant case) gp96 immunosuppression did not depend on the tissue used for isolation, and hsp 90s are highly conserved. Lindquist et al. (1998, IDS) is cited.

The Inventor's arguments, assertions, and opinions are acknowledged. They do not however, address all of the issues that necessitated the instant rejection. The claims recite little more than the administration of an hsp90 (or hsp70) for the inhibition of rejection. And the specification discloses little regarding the "relatively high doses" now discussed by the Inventor. See the single paragraph bridging pages 31 and 32 which indicates that doses in the range of 100-200 um of gp96 for a 20-25 g mouse prevent graft rejection. "Similar high dosages of 100-200 ug, or more than 200 ug, of hsp may also be effective in the treatment of larger mammals including humans". This comprises the *entire* disclosure of the specification regarding effective dosages in humans. Said disclosure cannot be considered to be enabling. Additionally note that Claim 46 actually recites what would be considered a relatively low dose, 5 ug. Given the undisputed fact that hsps can also be

immunostimulatory, see for example, the Inventor's own work, Chandawarkar et al., 2004, Exhibit B, "depending upon the dose of immunization used, gp96 may elicit an antigen-specific immune response …" (page 615, column 2), such a minimal disclosure cannot be considered to be enabling of the claimed method, particularly in view of the fact that an inappropriate dosage of hsp would not merely be ineffective, but potentially fatal in that it could exacerbate the condition for which treatment is intended. Clearly, the dosage issue comprises a critical component of the claimed invention and accordingly must be disclosed adequately in the instant specification.

Regarding the Inventor's assertions that all species and all hsp90s can be immunosuppressive, the Inventor's opinion alone is not persuasive. Given that the use of hsps for immunosuppression *is* the instant invention, in the absence of data, at the very least, sound scientific reasoning would be required to support the Inventor's assertions. The Inventor asserts that because gp96 immunosuppression did not depend on the tissue from which it was derived, all hsp90s would be immunosuppressive. It is unclear how this conclusion can be drawn. The source of a single hsp says nothing regarding all hsps from all sources. Also note that Lindquist et al. teaches nothing regarding the immunosuppressive nature of hsps. The work concludes, "This review focuses on the role of hsps and related proteins in normal growth". Thus, it is unclear how the Inventor believes this reference supports the method of the instant claims.

The Inventor cites WO 02/072133 as support for the assertion that all hsp70s would inhibit graft rejection. A review of the reference reveals that the minimal data does not necessarily support the Inventor's broad assertions. While the reference does show that under certain conditions BiP can induce properties that might be considered indicative of immunosuppression, the Examiner has made of record instances wherein IL-10 is not necessarily immunoprotective, a shift towards TH2 is not necessarily desirable, and a HSP70 might actually be a facilitator in numerous models of TH1-mediated pathology (see above). Accordingly, the net result must be a finding of unpredictability, particularly as the claims recite simply the administration of any hsp70 to inhibit the rejection of any graft in any embodiment, and the specification offers little additional guidance.

The Inventor argues that because the dosages required for immune stimulation have been investigated, the findings there, e.g., U.S. Patent 5,837,251, can be applied to the instant invention.

This seems a curious argument in light of Applicant's sound rejection of, and objection to, the Examiner's use of similar logic. See for example, Applicant's response of 9/09/02 wherein Applicant argued that findings regarding the immunostimulatory nature of hsps cannot be applied to immunosuppressive hsps. The Inventor's argument is also inconsistent with Applicant's attorney's instant remarks at page 6.

Regarding Applicant's additional arguments, at page 14 Applicant cites the Office's Utility Guidelines.

Applicant is reminded that no rejection for lack of utility has been made.

Applicant argues that the Examiner's conclusion that the genetic source of the gp96 used in immunosuppression is relevant does not logically follow the observations cited. Applicant notes that the dosages of rat and mouse gp96 complex in Experiment 2 were not the same.

The Examiner's logic is that if mouse gp96 appears to have some immunosuppressive activity in transplanted mice, but rat gp96 does not, the source of the gp96 would then appear to be relevant in the context of the transplant host. Regarding the dosages of rat and mouse gp96 employed, the dosages were chosen by Applicant.

Applicant cites Chandawarkar (2004) in support of the claimed method.

A review of Chandawarkar et al. (2004) as well as Chandawarkar et al. (1999) is enlightening. Chandawarkar et al. (1999) teaches that the source of the gp96 complex is indeed critical to its immunosuppressive properties, see Figure 3B, "Immunization with high doses (10 mg i.d.) of Meth A gp96 but not liver gp96 elicits concomitant immunity to Meth A sarcoma", i.e., liver gp96 was not immunosuppressive in a Meth A tumor graft context. Thus, at the time of filing, the method of the instant claims was clearly not enabled in its breadth. Chandawarkar et al. (2004) teaches that the results of the 1999

work were due to "differences in experimental design" and "interpretation". The newer work teaches that it was later discovered that an immunizing dose (in this case Meth A, or in the context of the method of the instant claims, the cell, tissue or organ graft antigens for which inhibition against rejection is desired) *must* be administered before the suppressive high dose of gp96 is administered (page 617, column 1). This is clearly not a consideration addressed by the instant specification. It would seem then that the Inventor's own work demonstrates that immunosuppression employing hsps, in the context of the inhibition of graft rejection, comprises a much more complex issue than is disclosed in the instant specification, requiring consideration of numerous issues that are not disclosed in the specification. Accordingly, the specification cannot be considered to be enabling of the method of the instant claims.

Applicant argues that hsp70 hsps are enabled by WO 02/072133 and that the evidence provided by the Examiner does not suggest that "the disclosure of the '133 publication does not enable the use of Bip for suppression of immune responses".

Applicant's arguments are acknowledged. While the disclosure of the '133 publication may enable the use of Bip for suppression of immune responses in specific contexts, it does not enable the broad methods of the instant claims. The simple showing of the suppression of an *in vitro* allogeneic response is not representative of the claimed method. Interestingly, the reference states that Bip must be administered before transplant (page 22), seemingly at odds with the Inventors' teaching, Chandawarkar et al. (2004), that the rejection antigens must be administered before the immunosuppressive hsp.

Applicant has essentially dismissed the references provided by the Examiner by arguing that the specific contexts of the teachings of each are irrelevant to the method of the instant claims. It remains the Examiner's position that the references teach what they teach - "The combined references indicate that, at best, the use of a HSP70 in a method of inhibiting a TH1-mediated response [including graft rejection] must be considered to be highly unpredictable" for the reasons set forth above. Also note that it appears inconsistent to argue that the references offered in support of the claimed invention must be applied broadly, but the references used in a showing of a lack of broad enablement must be applied very narrowly.

Applicant discounts the Examiner's characterization of the models of WO 02/072133 and the possible mechanisms underlying the possible nature of immunosuppression by hsps.

The Examiner has addressed above the limited nature of the teachings of WO 02/072133. Applicant is advised that absent an attempt to understand the underlying mechanisms through which an invention functions it is essentially impossible to extrapolate additional undisclosed results and determine the enabled range of an invention. Merely attacking the individual references provided by the Examiner does not in itself enable the method of the instant claims. Even assuming that the findings of the references cannot be applied to the instant case, Applicant still faces the problems set forth above, e.g., the undisputed fact that in certain embodiments encompassed by the claims the administration of Hsps is actually immunostimulatory, as well as a lack of guidance in the specification regarding the determination of proper doses for possible immunosuppression versus certain immunostimulation, as well as conflicting teachings and unaddressed considerations of WO 02/072133, Chandawarkar et al. (1999), and Chandawarkar et al. (2004).

6. The following are new grounds for rejection.

7. Claim 53 is rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically, a method wherein the hsp is not an alloantigen of the grafted cell, tissue or organ.

Applicant indicates that support for the new amendment can be found at pages 7 and 9 of the specification. A review of the cites shows support only for a method wherein the alloantigen is not a grafted tissue (page 9, line 35).

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 33, 35, 38, 40, 44, and 50 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Srivastava et al. (1986, IDS).

Srivastava et al. teaches a method of inhibiting the rejection of a grafted cell (Meth A sarcoma) comprising administering a purified gp96 hsp complex to a mouse before the Meth A cells are grafted (see particularly page 3410, Figure 5, "20 units").

The reference teaching anticipates the claimed invention.

10. Applicant's amendment or action necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's

voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

13. **Please Note**: Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). Inquiries of a general nature may also be directed to the Technology Center 1600 Receptionist at (571) 272-1600.

12/27/05

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